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(71) Applicant: **CZECHOSLOVAK ACADEMY OF SCIENCES**
Narodni 3
111 42 Praha Stare Mesto(CS)

(72) Inventor: **Cejkova, Jitka, c/o Czechosl. Academy of Sciences**
Narodni 3
CS-11142 Praha Stare Mesto(CS)
Inventor: **Vacik, Jiri, c/o Czechosl. Academy of Sciences**
Narodni 3
CS-11142 Praha Stare Mesto(CS)
Inventor: **Lojda, Zdenek, c/o Czechosl. Academy of Sciences**
Narodni 3
CS-11142 Praha Stare Mesto(CS)

(74) Representative: **Overbury, Richard Douglas**
Haseltine Lake & Co Hazlitt House 28, Southampton Buildings Chancery Lane
London WC2A 1AT(GB)

(54) Use of protease inhibitors as antiexudative, antiphlogistic and antimicrobial agents.

(57) A medcamentous form with antiexudation, antiphlogistic and antimicrobial effects in an aqueous or ointment base, suitable above all as an ophthalmologic, otolaryngologic, or dermatologic drug, which contains inhibitors or proteases, as are aprotinin, soyabean trypsine inhibitor, and elastatinal, either single or in a combination, in the amount of 0.1 mg to 20 mg per 1 ml of physiological saline or buffer solution, which is preferably ionically balanced and has pH 6.5 to 7.5, pr per 1 g of ointment base.

The medicamentous form may further contain 0.05 to 1.5 wt.-% of steroidal antiphlogistics, for example, dexamethasone, and/or 0.05 to 5 wt.% of nonsteroidal antiphlogistics, for example, indomethacin, and/or 0.2 to 1 wt.-% of antibiotics suppressing the growth of microbes, as are, for example, neomycin, bacitracin, chloramphenicol, tetracycline.

EP 0 420 600 A2

PHARMACEUTICALLY ACTIVE COMPOSITION

The invention pertains pharmaceutically active composition and more particularly to a medicamentous form of the composition for external use and having strong antiexudation, antiphlogistic, and antimicrobial effects. The composition is preferably provided in a suitable aqueous or ointment base and is applicable, for example, as an ophthalmologic, otolaryngologic, or dermatologic drug.

Arachidic acid is liberated in damaged, wounded or inflamed tissues from phospholipids of cytoplasmatic membranes by the action of phospholipase enzyme, and may be then metabolized by the cyclooxygenase cycle (by cyclooxygenase enzyme) or lipooxygenase cycle (by lipooxygenase enzyme) to prostanoids and eicosanoids.

Antiphlogistics of both the steroid and nonsteroid nature, antibiotics, and sulfonamides are often used for therapeutic purposes. The antibiotics, which specifically suppress pathogenic microbes and which are most often used in ophthalmology, include tetracycline, chloramphenicol, bacitracin, and neomycin. Therapeutic substances which prevent the development of inflammation (antiphlogistics) are known in both steroidal and nonsteroidal forms. The steroidal antiphlogistics (for example dexamethasone) block in particular phospholipase. The antiinflammatory drugs of nonsteroid nature (e.g., indomethacin, flurbiprofen, pirprofen) block in particular cyclooxygenase. The blockade of these enzymes is important, because the products formed in metabolic cycles have a strong chemotactic effect (they cause accumulation of leucocytes in the sites of origin) (e.g., some leucotrienes) and increase the vascular permeability. This contributes to an excessive development of the inflammation. Inflammations (both of infectious and noninfectious origin) are very dangerous for the anterior and posterior segments of the eye. Thus, scars formed in the cornea as the final stage of healing processes cause the loss of an exceptional function of this tissue, i.e. of its transparency. The loss of transparency of optical media of eye (cornea, lens) then leads to the reduction or even loss of sight.

Disadvantages of locally applied conventional antiphlogistics are their relatively low efficiency, retardation of healing, and their contribution to the development of infection. The local effect of antibiotics has been found to be limited and, moreover, there is a danger of the development of an allergic reaction. A higher concentration of antibiotics, which is necessary for obtaining the healing effect in many cases, can have toxic effects on the tissue. For this reason, a local treatment with antibiotics is commonly supplemented by a general administration of antibiotics, which has disastrous consequences with respect to the suppression of antibody. formation and the ability of the organism to combat infection. This is why new methods of treatment are desirable. One of the very prospective possibilities of treatment is the inhibition of plasmin and other destruction proteases (e.g., collagenase or elastase) with specific inhibitors. The said enzymes either directly develop the destruction processes (e.g., plasmin) or enable these processes by own activity (e.g., collagenase, elastase). However, plasmin is effective not only as an initiator developing the degeneration processes proceeding in cascades, but also contributes to an excessive development of inflammations by several other mechanisms, of which at least chemotaxis should be mentioned.

Amongst others, plasmin may be inhibited with aprotinin. This substance when administered in an aqueous solution and low concentrations has been successfully used in the treatment of some lesions of the anterior segment of eye. The authors of this invention found, moreover, that aprotinin inhibits not only plasmin but also several other proteolytic enzymes (for example, leucocytic elastase), which contributes to the destruction processes.

Accordingly, the present invention seeks to provide a pharmaceutically active composition in a medicamentous form, in an aqueous or ointment base, particularly suitable as opthalmologic, otolaryngologic, and dermatologic drug, which contains, inhibitors of proteases.

According to the present invention there is provided a pharmaceutically active composition having antiexudation, antiphlogistic and/or antimicrobial properties suitable for use as an ophthalmolgic, otolarynigologic or dermatologic medicament, having an aqueous or ointment base, characterised in that the composition comprises at least one inhibitor of proteases.

Examples of inhibitors of proteases according to the invention include aprotinin, soya-bean inhibitor of trypsine, and elastatinal preferably in a concentration of 0.1 to 20 mg per 1 ml of solution or 1 g of ointment base. These inhibitors may be applied either singly or in combination, dissolved in physiological saline or buffer solution with pH 6.5 to 7.5, which is advantageously ionically balanced (e.g., phosphate or borax buffer) or present in an ointment base.

The ionically balanced buffer solution means that sodium chloride is added to the buffer solution in such a way that the resulting solution is ionically balanced, for example, a precise formulation for a

borax buffer with pH 7.4 is as follows:
solution A - 1.9 g $Na_2P_4O_7$ per 100 ml H_2O pro injectione
B - 1.25 g H_3BO_3 + 0.3 g NaCl per 100 ml H_2O pro injectione
- 10 ml of solution A + 90 ml of solution B.

The medicamentous form according to the invention in liquid state may further advantageously contain 0.05 to 15 ωt.-% of thickeners selected from the group comprising hydroxypropyl methyl cellulose, methyl cellulose, polyvinylpyrrolidone, polyvinyl alcohol, poly(alklene glycols), poly/hydroxyalkyl(meth)acrylates or poly(meth)-acrylamides.

High concentrations of aprotinin, or also further inhibitors, locally applied can act not only curably with respect to the advanced stage of disease but also preventively, i.e. they prevent from formation of destrution processes if administered in time. The vehicles (thickeners) with protracted effect then enable a longer contact of the remedy (e.g. aprotinin) with the tissue.

The combination of aprotinin with other inhibitors, e.g. with elastatinal or inhibitor from soyabeans, enhances the therapeutic effect.

The pharmaceutically active composition according to the invention may advantageously further comprise 0.05 to 1.5 wt.-% of steroidal antiphlogistics, for example, indomethacin, and/or 0.2 to 1 wt.-% of antibiotics killing microbes, for example, bacitracin, neomycin, tetracycline, or chloramphenicol.

The combination of protease inhibitors with antiphlogistics or antibiotics or all the substances together increases the anti-inflammatory and antimicrobial effect (the inhibitors block some products of microbes, e.g., elastase and other proteases). This permits the use of antibiotics only locally and in smaller doses. The concentration of antiphlogistics may also be reduced and, at the same time, the therapeutic effect is greater and the time of treatment may be shorter, which is of particular importance for the healing of tissue.

The medicamentous form is most often applied by instillation or as an ointment into conjunctival sac. However, it can be also used for irrigation or lubrication of eye, facial sinuses, and external auditory meatus, and it may be injected into anterior eye chamber, and the like. The medicamentous form in the liquid state may be also be presented in a hydrophilic three-dimensional polymer matrix, advantageously in the form of a strip, contact lens, and the like, from which the active components are released. The incorporation of medicamentous form into a hydrophilic matrix may be performed according to the invention, for example, by conditioning of the matrix in the solution of the medicamentous form in order to attain the required concentration of inhibitors, or also with antiphlogistics and antibiotics in polymer matrix.

The pharmaceutically active composition according to the invention has a strong antiexudative, antiphlogistic and antimicrobial effect. Their therapeutic effects consist above all in the inhibition of plasmin, leucolytic elastase, and other serine proteases, and in the inhibited activation of latent forms of some endoproteases and several further subsequent reactions such as chemotaxis and vasculatisation of cornea. The invented pharmaceutically active composition, according to the invention, prevents in many cases from the development of some diseases and, in other cases, stops the development of disease.

The invention is further illustrated in the examples of performance, without limiting its scope to them.

Preparation of medicamentous form in liquid state:

Each substance is separately dissolved in a small amount (10 to 40 ml) of buffer or physiological saline.

Ointment base and ointment preparation:

10 g lanolin, 10 g liquid paraffin, and 80 g white petroleum jelly is melted in a water bath, the mixture is strained through hydrophilic gauze and then sterilized. If the therapeutics is easily soluble in water, it is dissolved in the necessary amount of distilled water for the preparation of injections, mixed with the ointment base in part molten form in a water bath and stirred until complete cooling. If the therapeutics is insoluble in water, it is used for the preparation in the finest powdered form and first triturated in a smaller amount of liquid paraffin and then mixed with the ointment base.

Example 1
Aprotinin 0.01 g
hydroxypropyl methyl cellulose 1 g
ionically balanced borax buffer of pH 7.4 up to 100 g
The drops when instilled into conjunctival sac in intervals of 3 h healed allergic conjunctivitis within 3 to 5 days.

Example 2
Aprotinin 0.005 g
hydroxypropyl methyl cellulose 2.5 g
ionically balanced phosphate buffer of pH 7.4 up to 100 g
The drops were instilled into conjunctival sac three times a day. Various cases of noninfectious conjunctivitis were healed within a week.

Example 3

Aprotinin 0.05 g
polyvinylpyrrolidone (mol. weight 360,000) 1 g
ionically balanced phosphate buffer of pH 7.2 up to 100 g
Defects of the corneal epithelium were healed within four days of administration of drops into conjunctival sac in intervals of 4 h.

Example 4

Aprotinin 0.005 g
polyvinylalcohol 1 g
ionically balanced borax buffer of pH 7.4 up to 100 g The drops applied into conjunctival sac in the intervals of 2 h healed minute wounds of conjunctiva, cornea, and eye lids within 2 to 4 days.

Example 5

Aprotinin 0.2 g
hydroxypropyl methyl cellulose 2.5 g
physiological saline up to 100 g
The etched and burnt cornea was healed during 4 days by application the drops four times a day. Transparency of the cornea was recovered either completely or at least on the periphery of cornea.

Example 6

Aprotinin 0.002 g
inhibitor from soya beans 2 g
ionically balanced borax buffer up to 100 g
The drops instilled into conjunctival sac in intervals of 2 h were successful for faster reepithelization after therapeutic abrasion of corneal epithelium.

Example 7

Aprotinin 0.025 g
elastatinal 0.005 g
hydroxypropyl methyl cellulose 2.5 g
ionically balanced borax buffer up to 100 g
The drops applied into conjunctival sac each 4 hours were successfully used for the treatment of corneal infiltrates which disappeared during a week.

Example 8

Aprotinin 0.004 g
inhibitor from soya beans 0.1 g
hydroxypropyl methyl cellulose 1.5 g
elastatinal 0.01 g
ionically balanced phosphate buffer up to 100 g
The drops were used for the treatment of cornea etched with concentrated acids and hydroxides. The cornea healed during a month and the transparency was recovered either completely or in part.

Example 9

Aprotinin 0.01 g
dexamethasone sodium phosphate 0.1 g
hydroxypropyl methyl cellulose 2.5 g
ionically balanced borax buffer up to 100 g
The eye drops healed severe allergic conjunctivitis by instillation three times a day.

Example 10

Aprotinin 0.1 g
dexamethasone sodium phosphate 0.5 g
hydroxypropyl methyl cellulose 2 g
ionically balanced phosphate buffer up to 100 g
The drops were instilled into the conjunctival sac 3 times a day. Ulcers of the cornea with various origin healed during a week.

Example 11

Aprotinin 0.1 g
elastatinal 0.01 g
prednisolone acetate 0.02 g
polyvinylpyrrolidone (mol. weight 360,000) 1 g
ionically balanced phosphate buffer of pH 7.4 up to 100 g
The drops were instilled 4 times a day for treatment of deep corneal infiltrates. Healing occurred within a week. In the cases complicated with a secondary inflammation of the iris, also this inflammation disappeared during a week.

Example 12

Aprotinin 0.05 g
indomethacin 1 g
hydroxypropyl methyl cellulose 2.5 g
ionically balanced phosphate buffer (pH 7.4) up to 100 g
The drops were instilled 4 times a day. The symptoms of irritation of eye balls after extraction of cataract receded during several days.

Example 13

Aprotinin 0.1 g
diclofenac 0.05 g
hydroxypropyl methyl cellulose 3 g ionically balanced borax buffer up to 100 g The drops instilled into conjunctival sac 4 times a day prevented from the vascularisation of cornea caused by wearing hydrophilic contact lenses.

Example 14

Aprotinin 0.05 g
flurbiprofen 0.1 g
hydroxypropyl methyl cellulose 3 g
ionically balanced phosphate buffer of pH 7.2 up to 100 g
The drops were instilled into conjunctival sac in the internals of 4 h. Defects of the corneal epithelium healed within several days. In other cases, the drops were successfully used for the inhibition of vasculatisation of the cornea after application of contact lenses.

Example 15

Aprotinin 1 g
dexamethasone sodium phosphate 0.1 g
indomethacin 1 g
elastatinal 0.1 g
A contact lens comprising HEMA - DEGMA (the crosslinked copolymer of 2-hydroxyethyl methacrylate with diethylene glycol methacrylate

containing 55 wt.-% of equilibrium water) was applied on the eye etched with strong alkalies and the drops were instilled over the contact lens in intervals of 4 h. The lesion healed during 3 weeks.

Example 16

Aprotinin 0.5 g
neomycin sulfate 0.35 g
hydroxypropyl methyl cellulose 2.5 g
ionically balanced phosphate buffer (pH 7.2) up to 100 g

The drops were instilled in intervals of 3 h at bacterial keratitis. The corneae afflicted by the infection of Pseudomonas aeruginosa healed during 5 days.

Example 17

Aprotinin 0.75 g
chloramphenicol 0.5 g
indomethacin 1 g
hydroxypropyl methyl cellulose 3 g
ionically balanced borax buffer (pH 7.2) up to 100 g The drops were applied 3 times a day for the treatment of nonhealing corneal ulcers. The cornea healed during a week.

Example 18

Aprotinin 1 g
tetracycline 0.3 g
elastatinal 0.2 g
flurbiprofen 0.5 g
hydroxypropyl methyl cellulose 3 g
ionically balanced phosphate buffer (pH 7.4) up to 100 g

The drops were instilled in intervals of 3 h into eyes etched with concentrated hydroxides. The cornea did not break down and healed with a scar during a month.

Example 19

Elastatinal 0.5 g
dexamethasone sodium phosphate 0.1 g
polyvinylalcohol 2 g
physiological saline up to 100 g

The drops were instilled into conjunctival sac in intervals of 3 h. Perforation of the cornea healed during a week.

Example 20

Elastatinal 0.3 g
soya-bean inhibitor of trypsine 0.2 g
hydroxypropyl methyl cellulose 2 g
ionically balanced phosphate buffer (pH 7.4) up to 100 g

The drops were instilled into conjunctival sac 4 times a day. Defects of the corneal epithelium healed during a week.

Example 21

Aprotinin 0.1 g
elastatinal 0.05 g
dexamethasone sodium phosphate 0.1 g
chloramphenical 0.5 g
physiological saline up to 100 g

The solution was successfully used in the treatment of rhinal allergoses and allergoses of meatus acusticus externus.

Example 22

Aprotinin 0.25 g
prednisolon acetate 0.025 g
neomycin sulfate 0.015 g
ointment base up to 5 g

The ointment was applied into the conjunctival sac in intervals of 4 h; both surface and deep corneal inflammation healed within a week. In other cases, the ointment was very efficient in the treatment of infected wounds of skin.

Example 23

Elastatinal 0.1 g
aprotinin 0.1 g
dexamethasone sulfate 0.15 g
flurbiprofen 0.1 g
chloramphenicol
physiological saline up to 100 g

A contact lense made from the crosslinked copolymer of 2-hydroxyethyl methacrylate and diethylene glycol methacrylate (HEMA - DEGMA) (55 wt.-% of equilibrium water content) was swelled in this solution for 24 h. The contact lens was used for the treatment of corneae burned with alkalis and lime. The healing ad integram occurred in some cases; in more severe cases, where the cornea usually had broken down, the tissue after the application of lenses healed with a scar. In other cases, the contact lens proved very suitable for the treatment of corneal ulcers.

Example 24

Aprotinin 1 g
elastatinal 0.1 g
flurbiprofen 0.1 g
dexamethasone sodium phosphate 0.1 g
neomycin sulphate
physiological saline up to 100 g

A contact lens from the crosslinked polymer of 2-hydroxyethyl methacrylate (38 wt.-% of equilibrium water) was swelled in the given solution for 24 h. The contact lens was used for the treatment of non-healing corneal erosions. Within a week after application, the reepithalization was sped up. Extra-ordinary results were attained after severe etching and burning of the anterior segment of eye. An intraocular inflammation did not develop, the cornea did not exhibit ulceration and healed with a scar during a month. The transparency recovered in the periphery of corneae.

Example 25

Aprotinin 0.02 g
elastatinal 0.05 g
dexamethasone sulphate 0.1 g

chloramphenicol 0.2 g
ionically balanced phosphate buffer (pH 7.4) up to 100 g
A strip from HEMA - DEGMA material (55 wt.-% of equilibrium water content) was immersed for 24 h into the solution of the above given composition and then applied into the lower fornix of the eye. After 24 h, the strip was removed from eye, immersed into the given solution overnight, and applied again. Corneal ulcers of various origin were healed after a week of treatment (application).

Claims

1. A pharmaceutically active composition having antiexudation, antiphlogistic and/or antimicrobial properties suitable for use as an ophthalmolgic, otolarynigologic or dermatologic medicament, having an aqueous or ointment base, characterised in that the composition comprises at least one inhibitor of proteases.
2. A composition as claimed in claim 1 wherein the inhibitor of proteases is aprotinin, soyabean trypsine inhibitor or elastatinal.
3. A composition as claimed in claim 1 or 2 wherein the composition comprises from 0.1 mg to 20 mg of inhibitor of proteases per 1 ml of physiological saline or buffer solution.
4. A composition as claimed in claim 3 wherein the buffer solution is ionically balanced and has a pH in the range of from 6.5 to 7.5.
5. A composition as claimed in claim 1 or 2 which composition comprises from 0.1 mg to 20 mg of inhibitor of proteases per 1 g of ointment base.
6. A composition as claimed in any preceding claim werein the composition further comprises from 0.05 to 1.5 wt% of a steroidal antiphlogistic agent.
7. A composition as claimed in claim 6 wherein the steroidal antiphlogistic agent is dexamethasone.
8. A composition as claimed in any preceding claim wherein the composition further comprises from 0.05 to 5 wt% of a non-steroidal antiphlogistic agent.
9. A composition as claimed in claim 8 wherein the non-steroidal antiphlogistic agent is indomethamin.
10. A composition as claimed in any preceding claim wherein the composition further comprises from 0.2 to 1 wt% of an antibiotic agent.
11. A composition as claimed in claim 10 wherein the antibiotic agent is neomycin, bacitracin, chloramphenicol or tetracycline.
12. A composition as claim d in any of claims 1 to 4 and 6 to 11, wherein the composition further comprises from 0.05 to 15 wt% of thickeners selected from hydroxypropyl methyl cellulose, methyl cellulose, polyvinylpyrrolidone, polyvinylalcohol, poly(alkylene glycols), poly[alkylene glycol (meth)-acrylates] and poly(meth)acrylamides.
13. A composition as claimed in any of claims 1 to 4 and 6 to 12 when present in a hydrophilic matrix, which matrix is advantageously in the form of a strip or contact lens.
14. The use of the composition of any of claims 1 to 12 as an antiexudation, antiphlogistic and/or antimicrobial ophthalmologic, otolaryngologic or dermatologic treatment.

Claims for the following Contracting States:

1. A methof of preparing a pharmaceutically active composition having antiexudation, antiphlogistic and/or antimicrobal properties suitable for use as an ophthalmologic otolaryngologic or dermatologic medicament characterised in that the method comprises admixing at least one inhibitor of proteases and an aqueous or ointment base.
2. A method as claimed in claim 1 wherein the inhibitor of proteases is aprotinin, soya bean trypsine or elastatinal.
3. A method as claimed in claim 1 or 2 wherein the composition comprises from 0.1 mg to 20 mg of the inhibitor of proteases per 1 ml of physiological saline or buffer solution.
4. A method as claimed in claim 3 wherein the buffer solution is ionically balanced and has a pH in the range of from 6.5 to 7.5.
5. A method as claimed in claim 1 or 2 wherein the composition comprises from 0.1 mg to 20 mg of the inhibitor of proteases per 1 g of ointment base.
6. A method as claimed in any preceding claim which method further comprises admixing in the composition from 0.05 to 1.5 w.t% of a steroidal antiphlogistic agent.
7. A method as claimed in claim 6 wherein the steroidal antiphlogistic agent is indomethacin.
8. A method as claimed in any preceding claim which method further comprises admixing in the composition from 0.05 to 5 wt% of a non-steroidal antiphlogistic agent.
9. A method as claimed in claim 8 wherein the non-sertoidal antiphlogistic agent is indomethacin.
10. A method as claimed in any preceding claim which method further comprises admixing in the composition from 0.2 to 1 wt% of an antibiotic agent.
11. A method as claimed in claim 10 wherein the antibiotic agent is neomycin, bacitracin, chloramphenicol or tetracycline.
12. A method as claimed in any of claims 1 to 4 and 6 to 11 which method further comprises admixing in the composition from 0.05 to 15 wt% of at least one thickener selected from hydroxypropyl methyl cellulose, methyl cellulose, polyvinylpyrol-

lidone, polyvinylalcohol, poly(alkylene glycols), poly[alkylene glycol(meth)acrylates] and poly-(meth)acrylamides.

13. A method as claimed in any of claims 1 to 4 and 6 to 12 which method further comprises impregnating the composition into a hydrophilic matrix, which matrix is advantageously in the form of a strip of contact lens.

14. The use of the composition of any of claims 1 to 12 as an antiexudation, antiphlogistic and/or antimicrobial ophthalmologic, otolaryngologic or dermatologic treatment.

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(71) Applicant: **CZECHOSLOVAK ACADEMY OF SCIENCES**
Narodni 3
111 42 Praha Stare Mesto(CS)

(72) Inventor: **Cejkova, Jitka, c/o Czechosl. Academy of Sciences**
Narodni 3
CS-11142 Praha Stare Mesto(CS)
Inventor: **Vacik, Jiri, c/o Czechosl. Academy of Sciences**
Narodni 3
CS-11142 Praha Stare Mesto(CS)
Inventor: **Lojda, Zdenek, c/o Czechosl. Academy of Sciences**
Narodni 3
CS-11142 Praha Stare Mesto(CS)

(74) Representative: **Overbury, Richard Douglas**
Haseltine Lake & Co Hazlitt House 28, Southampton Buildings Chancery Lane
London WC2A 1AT(GB)

(54) **Use of protease inhibitors as antiexudative, antiphlogistic and antimicrobial agents.**

(57) A medcamentous form with antiexudation, antiphlogistic and antimicrobial effects in an aqueous or ointment base, suitable above all as an ophthalmologic, otolaryngologic, or dermatologic drug, which contains inhibitors or proteases, as are aprotinin, soyabean trypsine inhibitor, and elastatinal, either single or in a combination, in the amount of 0.1 mg to 20 mg per 1 ml of physiological saline or buffer solution, which is preferably ionically balanced and has pH 6.5 to 7.5, pr per 1 g of ointment base.

The medicamentous form may further contain 0.05 to 1.5 wt.-% of steroidal antiphlogistics, for example, dexamethasone, and/or 0.05 to 5 wt.% of nonsteroidal antiphlogistics, for example, indomethacin, and/or 0.2 to 1 wt.-% of antibiotics suppressing the growth of microbes, as are, for example, neomycin, bacitracin, chloramphenicol, tetracycline.

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European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 31 0516

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	AMERICAN JOURNAL OF OTOLARYNGOLOGY, vol. 9, no. 3, 1988, pages 142-148; W.B. Saunders Comp.; Y. HAMAGUCHI et al.: "Antiinflammatory effects of a corticosteroid and protease inhibitor agents on antigen-induced otitis media in Chinchillas" * Entire article * ---	1,2,14	A 61 K 31/00 A 61 K 37/64
X	EP-A-0 223 254 (LABSYSTEMS) * Entire document, esp. pages 8 and 9; claims * ---	1-3,14	
A	JOURNAL OF PHARMACOBIO-DYNAMICS, vol. 5, no. 5, May 1982, Pharmaceutical Soc. of Japan, pages 319-327; H. NAKAGAWA et al.: "Effect of proteinase inhibitors having anti-inflammatory activity on gelatinase, elastase and cathepsin G isolated from rat polymorphonuclear leukocytes" ---		TECHNICAL FIELDS SEARCHED (Int. Cl.5)
A	BIOCHEMICAL PHARMACOLOGY, vol. 32, no. 1, 1st April 1983, Pergamon Press, pages 1191-1195; H. NAKAGAWA et al.: "Anti-inflammatory effect of proteinase inhibitors on carrageenin-induced inflammation in rats" -----		A 61 K

~~The present search report has been drawn up for all claims~~

Place of search	Date of completion of the search	Examiner
THE HAGUE	28-08-1992	KLAVER T.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

European Patent Office

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid,

namely claims:

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions,
namely:

see sheet -B-

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☒ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid,

namely claims: 1-5,12-14

☐ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims.

namely claims:

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims 1 and 2-5,12-14 partially: Use of a protease inhibitor, esp. aprotinin for ophthalmologic, otolaryngologic and dermatologic treatment.

2. Claims 2-5,12-14 partially: Use of soy bean trypsine inhibitor as above.

3. Claims 2-5,12-14 partially: Use of elastatinal as above.

4. Claims 6-11: Combination preparations of a proteinase inhibitor with a steroid, a NSAIA or/and an antibiotic.